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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/590,991	06/09/2000	John E. Adamou	469201-475	2154

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ART UNIT	PAPER NUMBER
1645	6

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Please find below and/or attached an Office communication concerning this application or proceeding...

Office Action Summary

Application No.	Applicant(s)
09/590,991	Adamou et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 5, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above, claim(s) *5-15 and 17-22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4 and 16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election

1) Acknowledgment is made of Applicants' election, with traverse, of invention II, claims 25-34, filed 10/05/01 (paper no. 5) in response to the restriction requirement mailed 08/29/01 (paper no. 4).

The Applicants' traversal is on the grounds that many of the invention groups are related in that the method claims employ SEQ ID NO: 6 of invention I. Applicants argue that a search for SEQ NO: 6 would "necessarily" turn up the polypeptide, antibodies and a vaccine (comprising a microorganism) and methods of use of the polypeptide sequence.

Applicants' arguments have been carefully considered, but are not persuasive. As clearly set forth in the restriction requirement mailed 08/29/01, the products of inventions I, III and IX are structurally and/or biologically distinct from one another and belong to distinct classes. A search performed for one does not necessarily turn up art on the other. However, since Applicants have elected the product of invention I, claims 17 and 18, drawn to a method of use of the product of invention I, will be retained as pending claims pursuant to the rejoinder provisions of M.P.E.P 821.04 and will be withdrawn from consideration until such time as the subject matter of claims 1-4 are deemed allowable. The Examiner in charge of the instant application will then determine if claims 17 and 18 include all of the limitations of the allowable product claims and are of the same scope as allowable product claims, prior to determining if rejoinder will be permitted under M.P.E.P 821.04.

Status of Claims

2) Claims 1-22 are pending.

Claims 5-15 and 17-22 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 1-4 and the linking claim 16 are under examination.

Drawings

3) The drawings are objected to under 37 C.F.R 1.84 because of the reasons set forth by the

Draftsperson in the attached Form PTO 948 (paper no. 6). Correction is required.

Priority

4) The instant application claims domestic priority to SN 08/138,453, filed 06/10/1999.

Specification - Informalities

5) The instant specification is objected to for the following reason(s):

(a) The drawing 3 is objected to by the Examiner for lack of labeling of the two subparts or panels. The two panels of Figure 3 should be labeled as 3A and 3B. The figure description on page 5 of the specification should refer to the Figure as Figure 3A and 3B. Reference to these Figures throughout the specification should be amended accordingly.

(b) On page 34, lines 21 and 22, the address of the American Type Culture Collection is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this. It is suggested that Applicants examine the whole specification to make similar correction to the address, wherever it appears.

Rejection(s) under 35 U.S.C § 112, First Paragraph

6) Claims 1-4 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
  The breadth of the claims.

One or more of instant claims encompass a polypeptide comprising an amino acid sequence having "65%" or "80% or 95% identity" to the amino acid sequence as shown in SEQ ID NO: 6, fragments thereof and a vaccine comprising the same. However, the instant specification does not provide enablement for a such a polypeptide or a fragment thereof and a vaccine comprising the same. There is no evidence within the instant specification showing that a polypeptide having an amino acid sequence that is 65% or 80% or 95% identical to the amino acid sequence of SEQ ID NO: 6 does have the ability to serve as a vaccine and is able to elicit 'protective' antibodies in an animal against the whole genus *Streptococcus*.

The specification fails to teach the precise structural composition and the functional or biological characteristics of the claimed polypeptide variants. There is lack of disclosure as to which specific 65%, 70% or 95% identical regions of SEQ ID NO: 6 the claimed polypeptide variant encompasses. It is uncertain whether retention of 65%, 70% or 95% identical regions from any part of SEQ ID NO: 6 (i.e., terminal or central parts) would yield a polypeptide that would have the expected biologic, immunogenic or protective functions. It is unlikely that a polypeptide having 65%, 70% or 95% identity to any part of SEQ ID NO: 6 would retain or have the desired anti-*Streptococcus* specificity. Without a disclosure of the specific amino acid residues contained within the claimed polypeptide, one of ordinary skill in the art cannot be sure of the sequences embraced by the claims and would not be able to make and use those polypeptide sequences as recited in the instant claims, without undue experimentation. One of ordinary skill in the art would not be able to make such polypeptide sequences and use as vaccines, because there is no disclosure as to what amino acid residues are embraced by the claims and whether such residues would be able to induce protective antibodies. This is critical in view of the following. Although the claimed polypeptide is said to have 65%, 70% or 95% identity with SEQ ID NO: 6, there is a 35%, 30% and 5% dissimilarity between SEQ ID NO: 6 and the claimed polypeptides, and the effects of these dissimilarities upon protein structure and function cannot be predicted. For instance, Bowie *et al.* (*Science* 247: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determines the shape and function of a

protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al.* also teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess *et al.* (*J. Cell Biol.* 111: 2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al.* (*Mol. Cellular Biol.* 1988, 8: 1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. All these references demonstrate that even a single amino acid substitution/deletion will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 35%, 30% or 5% dissimilarity to the polypeptide of SEQ ID NO: 6, the function of the claimed polypeptides could not be predicted, based on the sequence similarity or identity with SEQ ID NO: 6, nor would it be expected to be the same as that of the polypeptide of SEQ ID NO: 6. Therefore, due to the functional uncertainty, lack of sufficiently enabling disclosure and/or adequate guidance within the instant specification, lack of adequate working examples enabling the full scope of the claims, quantity of experimentation necessary and breadth of instant claims, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the full scope of the

invention. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

7) Claim 16 is rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for a vaccine containing a serotype 4 (Norway strain) *S. pneumoniae* polypeptide comprising an amino acid sequence of SEQ ID NO: 6 and a pharmaceutically acceptable carrier, wherein the polypeptide is present in an amount effective to elicit protective antibodies in a mammalian animal against challenge with a serotype of *S. pneumoniae,* does not reasonably provide enablement for such a vaccine comprising a non-serotype 4 *S. pneumoniae* polypeptide comprising the amino acid sequence of SEQ ID NO: 6 and a pharmaceutically acceptable carrier, wherein the polypeptide is present in an amount effective to elicit protective antibodies in any animal against challenge with any species of the genus *Streptococcus*, or any serotype of *S. pneumoniae* other than serotype 6B.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the claimed method is related to one or more polypeptide variants of SEQ ID NO: 6, obtained from a specific serotype of *S. pneumoniae*, i.e., serotype 4, which induce protective antibodies. However, the scope of the claim broadly encompasses elicitation of protective antibodies by the polypeptide variant(s) in any animal against any organism of the genus *Streptococcus*. The instant specification, for example, at Figure 1, shows that a vaccine comprising an effective amount of a polypeptide comprising an amino acid sequence that is 100% identical to SEQ ID NO: 6 of serotype 4 (Norway strain) *S. pneumoniae* and a

pharmaceutically acceptable carrier, elicits protective antibodies in a mammalian animal against challenge with serotype 6B *S. pneumoniae,* strain SJ2. The limitation 'animal' encompasses an animal that is vertebrate, non-vertebrate, mammalian, non-mammalian, multicellular, transgenic etc., The limitation, "an organism of the genus *Streptococcus*", encompasses multiple species of *Streptococcus*, such as, *S. pyogenes, S. mutans, S. viridans, S. agalactiae etc.,* and multiple serotypes of *Streptococcus,* including 23 serotypes of *S. pneumoniae.* However, there is no evidence in the instant specification showing that one or more polypeptide variants of SEQ ID NO: 6, obtained from serotype 4 of *S. pneumoniae*, or a non-serotype 4 *S. pneumoniae,* would indeed elicit "protective" antibodies in any animal against any species of the genus *Streptococcus* other than *S. pneumoniae*, or any serotype of *S. pneumoniae* other than serotype 6B. There is no showing that the claimed polypeptide variants are immunologically or biologically effective against all species of the genus *Streptococcus*, or all serotypes of *S. pneumoniae.* This is important because the ability of a microbial polypeptide or its variants to confer broad genus-wide, species-wide or serotype-wide protection is not predictable. There is no evidence that the polypeptide of SEQ ID NO: 6 is produced by all members or species of the genus *Streptococcus,* or by all serotypes of *S. pneumoniae* other than serotype 4. The evidence is clearly not commensurate in scope with the breadth of the claim. Absent concrete evidence showing that the claimed polypeptide (or its variant as claimed) is produced by all serotypes of *Streptococcus pneumoniae* and that it confers homologous and heterologous protection against any member of the genus *Streptococcus* or any serotype of *S. pneumoniae* other than 6B, claim 16 is viewed as being non-enabled with respect to its full scope. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 1-4 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and confusing in the recitation "a polypeptide, including immunogenic fragments thereof", because it is unclear whether the claimed vaccine includes one polypeptide having an amino acid sequence at least 65% identical to SEQ ID NO: 6, or whether the vaccine includes such a polypeptide and 'immunogenic fragments' of the polypeptide. Clarification/correction is requested.

(b) Claim 16 lacks proper antecedent basis for the recitation "said polypeptide" (line 6), because there are earlier recitations of "polypeptides" in the claim, but not of a "polypeptide".

(c) Claim 16 is confusing and/or lacks proper antecedent basis for the recitation: "*S. pneumoniae* polypeptides selected from the group consisting of the polypeptides of claims 1, 2, 3, 4 .....". Claim 16 depends from claim 1, 2, 3 or 4, which do not refer to the polypeptides as "*S. pneumoniae* polypeptides".

(d) Claims 2-4, which depend from claim 1, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

10) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11) Claims 1-3 are rejected under 35 U.S.C § 102(a) as being anticipated by Bethe *et al.* (EMPL AF127143, submitted February 1999).

The term "vaccine" in the instant claims is viewed as the intended use of the product.

Bethe *et al.* disclose a polypeptide having an amino acid sequence that is 96.8% (i.e., at

least 65%, 80% or 95%) identical to the amino acid sequence of SEQ ID NO: 6. See the enclosed search report.

Claims 1-3 are anticipated by Bethe *et al.*

12) Claims 1, 2 and 16 are rejected under 35 U.S.C § 102(b) as being anticipated by Kunsch *et al.* (WO 98/18930).

Kunsch *et al.* disclose a polypeptide having an amino acid sequence that is 94.6% (i.e., at least 65% or 80%) identical to the amino acid sequence of SEQ ID NO: 6. See the enclosed search report and Table 1 of Kunsch *et al.* A vaccine comprising the polypeptide or fragments thereof, together with a pharmaceutically acceptable carrier, diluent or excipient, wherein the polypeptide is present in an amount effective to elicit a protective immune response to members of the *Streptococcus* genus in an animal, is taught (see pages 4 and 5; and claims 11, 12 and 16).

Claims 1, 2 and 16 are anticipated by Kunsch *et al.*

Objection(s)

13) Claim 4 objected to for being dependent from a rejected claim.

Claim 16 is objected for including non-elected subject matter.

Remarks

14) Claims 1-4 and 16 stand rejected. The polypeptide comprising an amino acid sequence of SEQ ID NO: 6 is free of prior art currently of record.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

16) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which

would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 2001

S. DEVI, PH.D.
PRIMARY EXAMINER